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10/573,324	03/24/2006	Yasuhiko Shiina	P29546	4957

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
01/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/573,324	SHIINA ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/06, 5/09 and 6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. The amendment filed 10/26/09 has been entered into the record. Claims 11-14 have been cancelled. Claims 1-10 and 15-17 are pending and are under examination.

Information Disclosure Statement

2. The information disclosure statement filed 7/24/06, 5/8/09 and 6/17/09 have been considered and initialed copies are enclosed.

Claim Objections Withdrawn

3. The objection to claims 1-7 is withdrawn in view of the amendment to spell out the full meaning of "L-PDGS".

Rejections Withdrawn

4. The rejection of claims 1-10 under 35 U.S.C. 112, first paragraph (scope of enablement) is withdrawn in view of the amendment to the claims. See new rejection under 35 U.S.C. 112, first paragraph (scope of enablement) based on amendment below.

5. The rejection of claims 1-10 under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment to the claims.

6. The rejection of claims 1-10 under 35 U.S.C. 102(a) as being anticipated by Guild et al W) 2003/060465 published July 24, 2003 is withdrawn in view of the amendment to the claims to recite that the subject is "free of renal disease and/or ischemic heart disease".

7. The rejection of claims 1-10 under 35 U.S.C. 102(e) as being anticipated by Guild et al W) 2003/060465 published July 24, 2003 is withdrawn in view of the amendment to the claims to recite that the subject is "free of renal disease and/or ischemic heart disease".

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 1 and dependent claims are drawn to a method of detecting or differentiating rheumatoid arthritis, comprising:

measuring the level of human lipocalin-type prostaglandin D synthase (L-PGDS) in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

detecting or differentiating rheumatoid arthritis if the level of L-PGDS is higher in the sample collected from the subject free of renal disease and/or ischemic heart disease than it is in a healthy volunteer and/or in a patient with a joint disease other than rheumatoid arthritis.

Claim 3 and dependent claims are drawn to a method of determining the stage of disease with regard to rheumatoid arthritis, comprising:

measuring the level of human L-PGDS in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

determining the stage of disease with regard to rheumatoid arthritis, wherein L-PGDS concentration increases with advancement of the stage of disease.

Claim 5 and dependent claims are drawn to a method of determining the degree of dysfunction or severity with regard to rheumatoid arthritis, comprising:

measuring the level of human L-PGDS in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

determining the degree of dysfunction or severity with regard to rheumatoid arthritis, wherein L-PGDS concentration increases with advancement of the degree of dysfunction or severity.

Applicants were not in possession as of the time of filing of the instant methods of detecting or differentiating rheumatoid arthritis (RA) or method of determining the stage of disease with regard to RA or a method of determining the degree of

dysfunction or severity with regard to RA in which human LPDGS is measured in a sample collected from a subject free of renal disease and/or ischemic disease.

In pages 6-7 of the specification, the statement is made that "the present invention is described in the following [1]-[14]". [1]-[14] does not implicitly or explicitly state that the subject from which the sample is collected is free of renal disease and/or ischemic disease.

In the examples 1-4, p. 16-18, it is not indicated whether the subjects are free of renal disease and/or ischemic disease. Levels of LPDGS is measured and compared between healthy volunteers, patients with other types of arthritis and rheumatoid arthritis patients.

The background section providing background information of LPDGS teaches that one study teaches that LPGDS is detected in increased amounts in blood of advanced renal disease patient and another study teaches that LPGDS is increased in body fluid of ischemic heart disease patients. See p. 4-5. This however is not written description support for the method of claim 1, 3, 5 and their respective dependent claims as set forth above.

The background information teaching that one study links increased LPGDS to renal disease and another separate study linking increased LPGDS to ischemic heart disease does not reasonably provide support that Applicants were in possession as of filing of the instant methods (as claimed) of detecting or differentiating rheumatoid arthritis (RA) or method of determining the stage of disease with regard to RA or a method of determining the degree of dysfunction or severity with regard to RA in which human LPDGS is measured in a sample collected from a subject free of renal disease and/or ischemic disease.

9. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting or differentiating rheumatoid arthritis, a method of determining the stage of disease with regard to rheumatoid arthritis and determining the degree of dysfunction with regard to rheumatoid arthritis wherein the levels of human L-PGDS in a sample collected from a subject without renal or heart disease *or other diseases known to affect the levels of L-PGDS* is measured, wherein the levels of human L-PGDS measured compared and is higher than the levels of human L-PGDS in healthy volunteer or a patient who has a joint disease other than rheumatoid arthritis but does not have other diseases that have elevated LPGDS, does not reasonably provide enablement for the instant methods of detecting or differentiating rheumatoid arthritis, a method of determining the stage of disease with regard to rheumatoid arthritis and determining the degree of dysfunction with regard to rheumatoid arthritis as claimed. **This is a scope of enablement rejection.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 1 and dependent claims are drawn to a method of detecting or differentiating rheumatoid arthritis, comprising:

measuring the level of human lipocalin-type prostaglandin D synthase (L-PGDS) in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

detecting or differentiating rheumatoid arthritis if the level of L-PGDS is higher in the sample collected from the subject free of renal disease and/or ischemic heart disease than it is in a healthy volunteer and/or in a patient with a joint disease other than rheumatoid arthritis.

Claim 3 and dependent claims are drawn to a method of determining the stage of disease with regard to rheumatoid arthritis, comprising:

measuring the level of human L-PGDS in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

determining the stage of disease with regard to rheumatoid arthritis, wherein L-PGDS concentration increases with advancement of the stage of disease.

Claim 5 and dependent claims are drawn to a method of determining the degree of dysfunction or severity with regard to rheumatoid arthritis, comprising:

measuring the level of human L-PGDS in a sample collected from a subject free of renal disease and/or ischemic heart disease; and

determining the degree of dysfunction or severity with regard to rheumatoid arthritis, wherein L-PGDS concentration increases with advancement of the degree of dysfunction or severity.

The facts that should be considered in determining whether a specification is enabling or if it would require an undue amount of experimentation to practice the invention include 1) the quantity of experimentation necessary to make or use the invention based on the content of the disclosure, (2) the amount of direction or

guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, the factors that weigh more in making the instant enablement rejection are discussed below.

Nature of the Invention and Breadth of the claims

The claims require the detection of human L-PDGS (lipocalin type prostaglandin synthase) in any type of sample collected from any subject free of renal or ischemic heart disease so as to detect or differentiate rheumatoid arthritis, determine the stage of disease or degree of dysfunction with regards to rheumatoid arthritis. The claims do not specify that the subject have rheumatoid arthritis (RA) or are suspected to have RA , thus the scope covers detection of LPDGS in both subjects or subjects who have other diseases except for renal or ischemic heart disease.

The amount of direction or guidance presented and the presence or absence of working examples

The specification teaches that the concentrations of L-PGDS in the blood of rheumatoid arthritis patients are higher than those of healthy volunteers and that the L-PGDS in the blood of rheumatoid arthritis patients tend to increase as the disease progresses and the more the severity of the disease and that the LPGDS concentration in the blood of rheumatoid arthritis patients tend to be higher than those of with other joint disease. See fig.1-3 and example 1 p. 16.

The state of the prior art, predictability or unpredictability in the art

The art teaches that not only is Lipocalin type prostaglandin D synthase aka beta trace protein elevated in renal or ischemic heart disease (see specification p. 4 last bridging paragraph to p. 5 first paragraph) it also increases in the cerebrospinal fluid of patients recovering from organic damage to the central nervous system and those with pathological brain atrophy (Hiraoka et al. Electrophoresis 2001, 22, 3433-3437, see p. 3433 under introduction). The art teaches that LPGDS is mainly localized in the central nervous system and male genital organs and the human heart. It is secreted into cerebrospinal fluid, seminal plasma and plasma respectively as beta-trace. See Su et al Clin Chem Lab Med 2001; 39 (12):1198-1203, p. 1200 under discussion. Schlatterer et al (US 2004/0171095 9/2/04) teaches that in inflammation such as rheumatoid arthritis or encephalitis increased amounts of PGDS can be found in bodily fluids such as plasma, synovial fluid, cerebospinal fluid, urine or in the ejaculate. Su et al detects LPGDS in ovarian tumors and teaches that LPGDS may have a potential for the

diagnosis of ovarian tumor. See Su et al p. 1201 column 2 end of first incomplete paragraph and p. 1201 column 1 last paragraph.

Thus, a higher L-PGDS in samples such as CSF or ovarian tumors or brain tumors or encephalitis or breast tumors (See Su et al abstract) from subjects (free of renal disease or ischemic disease) with said CSF or ovarian tumors or brain tumors or breast tumors or encephalitis and comparing to same samples collected from healthy volunteers does not necessarily indicate RA because these other diseases have not been ruled out in the instant method.

Similarly, higher amounts of LPGDS in samples such as CSF or ovarian tumors or brain tumors or breast tumors or encephalitis (See Su et al abstract) from subjects (free of renal disease or ischemic disease) with said CSF or ovarian tumors or brain tumors or breast tumors does not necessarily indicate the stage of RA or the degree of dysfunction or severity of RA.

Thus, detection of, for example, high levels of L-PGDS in a sample such as CSF or tumor tissue or other body fluid collected from subjects without renal or ischemic heart disease but with organic damage to the central nervous system and those with pathological brain atrophy or encephalitis or brain tumors or ovarian tumors or breast tumors may not detect or diagnose rheumatoid arthritis or stage of disease or degree of dysfunction but maybe indicative of another disease (organic damage to the central nervous system and those with pathological brain atrophy or brain tumors or ovarian tumors or breast tumors or encephalitis) in which increased L-PGDS is a factor. This is

also the case for when measurement values of L-PGDS in said subjects are compared with values of L-PGDS in samples collected from healthy volunteers and/or patients with joint diseases other than rheumatoid arthritis. Comparison of L-PGDS levels to those of patients with rheumatoid arthritis who do not have all these confounding diseases such in which L-PGDS levels are elevated is a better indicator of whether a subject has rheumatoid arthritis. Furthermore, ruling out other diseases in said subject is also important as L-PGDS levels are elevated in other disease apart from renal or ischemic heart disease. The methods as claimed do not account for all these confounding factors specifically that there are other diseases apart from renal or ischemic heart disease in which LPGDS is also elevated.

Thus, taken together as a whole, one of ordinary skill in the art could conclude that a high level of L-PGDS in a subject wherein said subject does not have renal or heart disease or other diseases in which levels of L-PGDS are elevated is a diagnosis of rheumatoid arthritis when the levels of L-PGDS is higher compared to the levels of L-PGDS in patients known to healthy patients. While, the specification is enabling being enabling for a method of detecting or differentiating rheumatoid arthritis, a method of determining the stage of disease with regard to rheumatoid arthritis and determining the degree of dysfunction with regard to rheumatoid arthritis wherein the levels of human L-PGDS in a sample collected from a subject without renal or heart disease *or other diseases known to affect the levels of L-PGDS* is measured, wherein the levels of human L-PGDS measured compared and is higher to the levels of human L-PGDS in

healthy volunteer or a patient who has a joint disease other than rheumatoid arthritis but does not have other diseases that have elevated LPGDS, the specification is not enabling for the full scope of the claims as claimed as set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2, 3, 4, 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 2, 4 and 6, the basis of comparison with a predetermined cut-off value based on measurement values of human L-PGDS in samples collected from healthy volunteers and/or patients with joint diseases other than rheumatoid arthritis (claim 2) or a predetermined cut-off value based measurement values of human L-PGDS in samples collected from rheumatoid arthritis patients classified in accordance with stage of disease or degree of dysfunction (claims 4 and 6) is vague and indefinite. The specification does not specially provide a definition for these predetermined cut-off values and the claims do not set forth the above predetermined cut-off value and thus the scope of the claims is vague and indefinite.

As to claim 3, it is not clear how measuring the level of LPDGS in sample from a subject free of renal disease or ischemic heart disease determines the stage of disease

with regard to rheumatoid arthritis as there is no comparison with measurement values of the concentration of LPGDS in, for example, rheumatoid arthritis patients in different stages of the disease in the method steps so as to arrive at the indicated outcome stated "wherein L-PGDS concentration increases with advancement of the stage of disease.

As to claim 5, it is not clear how measuring the level of LPDGS in sample from a subject free of renal disease or ischemic heart disease determines the degree of dysfunction or severity with regard to rheumatoid arthritis as there is no comparison with measurement values of the concentration of LPGDS in, for example, rheumatoid arthritis patients in each degree of dysfunction or degree of severity in the method steps so as to arrive at the indicated outcome stated "wherein L-PGDS concentration increases with advancement of the stage of disease".

Status of Claims

Claims 1-10 and 15-17 are rejected. No claims allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645